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<p>(54) Title: <b>NEW CRYSTAL MODIFICATION III OF TORASEMIDE</b></p> <p>(57) Abstract</p> <p>The present invention relates to the characterization of a new crystal modification III of torasemide, to a process for the preparation thereof by the use of controlled acidifying of alkaline solutions of torasemide with inorganic or organic acids with or without addition of a crystal seed, to its use as a raw material for the preparation of the crystal modification I of torasemide and of pharmaceutically acceptable salts of torasemide as well as to pharmaceutical forms containing this new crystal modification III of torasemide.</p>			

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WO 00/20395

PCT/HR99/00023

1

**NEW CRYSTAL MODIFICATION III OF TORASEMIDE****International Patent Classification:** C 07 D 213/70; A 61 K 31/44

The present invention relates to a new crystal modification of N-(1-methylethyl aminocarbonyl)-4-(3-methyl-phenylamino)-3-pyridinesulfonamide (in the further text of the application designated by its generic name "torasemide"), particularly to a new crystal modification III of torasemide, to processes for its preparation, to its use as a raw material for the preparation of the crystal modification I of torasemide and of pharmaceutically acceptable salts of torasemide as well as to pharmaceutical forms containing the said new modification III of torasemide as the active ingredient.

Torasemide is a compound with interesting pharmacological properties, which is described in DE patent 25 16 025 (Example 71). As a diuretic of Henle's loop it is useful as an agent for preventing heart or heart tissue damages caused by metabolic or ionic abnormalities associated with ischemia, in the treatment of thrombosis, angina pectoris, asthma, hypertension, nephroedema, pulmonary edema, primary and secondary aldosteronism, Bartter's syndrome, tumours, glaucoma, decreasing of intraocular pressure, acute or chronic bronchitis, in the treatment of cerebral edema caused by trauma, ischemia, concussion of the brain, metastases or epileptic attacks and in the treatment of nasal infections caused by allergens.

The ability of a substance to exist in more than one crystal form is defined as polymorphism and these different crystal forms are named "polymorph modifications" or "polymorphs". In general, polymorphism is affected by the ability of a molecule of a substance to change its conformation or to form different intermolecular or intramolecular interactions, particularly hydrogen bonds, which is reflected in different atom arrangements in the crystal lattices of different polymorphs. Polymorphism is found in several organic compounds. Among medicaments polymorphism is found in

WO 00/20395

PCT/HR99/00023

2

about 70% of barbiturates, 60% of sulfonamides and 60% of steroids and about 50% of medicaments of the said classes are not present on the market in their most stable forms (T. Laird, Chemical Development and Scale-up in the Fine Chemical Industry, Principles and Practices, Course Manual, Scientific Update, Wyvern Cottage, 1996).

The different polymorphs of a substance possess different energies of the crystal lattice and, thus, in solid state they show different physical properties such as form, density, melting point, colour, stability, dissolution rate, milling facility, granulation, compacting etc., which in medicaments may affect the possibility of the preparation of pharmaceutical forms, their stability, dissolution and bioavailability and, consequently, their action.

Polymorphism of medicaments is the object of studies of interdisciplinar expert teams [J. Halebian, W. McCrone, *J. Pharm. Sci.* **58** (1969) 911; L. Borka, *Pharm. Acta Helv.* **66** (1991) 16; M. Kuhnert-Brandstätter, *Pharmazie* **51** (1996) 443; H. G. Brittain, *J. Pharm. Sci.* **86** (1997) 405; W. H. Streng, DDT 2 (1997) 415; K. Yoshii, *Chem. Pharm. Bull.* **45** (1997) 338, etc.] since a good knowledge of polymorphism represents a precondition for a critical observation of the whole process of medicament development. Thus, at deciding on the production of a pharmaceutical form in solid state and with regard to the dose size, stability, dissolution and anticipated action, it is necessary to determine the existence of all solid state forms (on the market some computer programmes can be found, e.g. »Polymorph« as a module of »Cerius2« programme, MSI Inc., USA) and to determine the stability, dissolution and thermodynamic properties of each of them. Only on the basis of these determinations the appropriate polymorph can be selected for the development of pharmaceutical formulations.

From the great number of such efforts only a few will be mentioned. Thus, Gordon et al. (US 4,476,248) protected a new crystal form of ibuprofen and a process for the preparation thereof; Bunnell et al. (EP 733 635) protected a new crystal form, a process for preparation thereof and a pharmaceutical formulation of the medicament

WO 00/20395

PCT/HR99/00023

3

olanzapine containing this new crystal form; R. B. Gandhi et al. (EP 749 969) protected a new process for the preparation of polymorph form I of stavudine from a mixture of one or more forms I, II and III; A. Caron et al. (EP 708 103) protected a new crystal form of irbesartane, a process for the preparation thereof and pharmaceutical formulations containing this crystal form.

It is known [*Acta Cryst. B34* (1978), 2659-2662 and *Acta Cryst. B34* (1978), 1304-1310] that torasemide can exist in two crystal modifications differing with regard to the parameters of a single cell, which is confirmed by X-ray diffraction on their monocrystals. Both modifications are formed simultaneously by the slow evaporation of the solvent from a solution of torasemide in a mixture petroleum ether/ethanol. The modification I with melting point 169°C crystallizes monoclinically in the space group P 2<sub>1</sub>/c (prisms), while the modification II with melting point 162°C crystallizes monoclinically in the space group P 2/n (foils). Additionally, for the modification I the melting point 169.22°C is stated in *Iyakuhin Kenkyu 25* (1994), 734-750.

According to Example 71 of DE 25 16 025 torasemide in a crystal form with melting point 163-164°C is obtained.

In US 4,743,693 and US reissue 34,580 or US 4,822,807 and US reissue 34,672 there is disclosed a process for the preparation of a stable modification I of torasemide from an unstable modification II of torasemide by adding a catalytic amount (1%) of a stable modification I of torasemide into a suspension of the unstable modification in water and stirring the mixture at a temperature from room temperature to 90°C within 3 hours to 14 days. In US 4,743,693 and US reissue 34,580 it is stated that the stable modification I of torasemide (monoclinic, space group P2<sub>1</sub>/c) has a melting point of 162°C and the unstable modification II of torasemide (monoclinic, space group P 2/n) has a melting point 169°C, which is contrary to the statements in *Acta Cryst. B34* (1978), 2659-2662, *Acta Cryst. B34* (1978), 1304-1310 and *Iyakuhin Kenkyu 25* (1994), 734-750.

WO 00/20395

PCT/HR99/00023

4

In the abstract of US 4,822,807 the authors ascribe the melting point 162°C to the stable polymorph I of torasemide and the melting point 169°C to the unstable polymorph II of torasemide, whereas in the claims of the said patent different melting points for either polymorph are stated, namely for polymorph I the melting point 169°C and for polymorph II the melting point 162°C.

In the abstract of US reissue 34,672 the authors ascribe the melting point 162°C to the pure modification I of torasemide and the melting point 169°C to the modification II of torasemide, whereas in the claims the melting point 159-161.5°C for the pure polymorph I and the melting point from about 157.5 to about 160°C for the unstable polymorph II are stated.

It has now been surprisingly found that by a controlled acidifying of alkaline solutions of torasemide with inorganic or organic acids with or without addition of a seed crystal at a temperature between 0 and 35°C within 15 minutes to 25 hours, a new crystal modification III of torasemide can be prepared.

By the alkaline solutions of torasemide according to the process of the present invention there are meant an alkaline extract of the original reaction mixture for the synthesis of torasemide, alkaline solutions of any crystal modification I, II or III of torasemide or alkaline solutions of any mutual mixtures of crystal modifications I, II or III of torasemide.

In the process of the present invention for the preparation of alkaline solutions of torasemide modifications, water solutions of lithium, sodium and potassium hydroxide as well as water solutions of sodium and potassium carbonate can be used.

The acidifying of the alkaline torasemide solutions according to the invention can be performed in inorganic acids such as hydrochloric, sulfuric, phosphoric and nitric acids and in organic acids such as formic, acetic, propionic, oxalic, tartaric, methanesulfonic and p-toluenesulfonic acids.

WO 00/20395

PCT/HR99/00023

## 5

As the seed crystal in the processes of the present invention crystal powder of one of the isostructure substances, particularly crystal powder of the crystal modification III of torasemide can be used.

It has additionally been found that by using the process of the present invention no decomposition of torasemide occurs and the impurities that may be present in the alkaline extract of the original reaction mixture for the synthesis of torasemide or in modifications I, II or III of torasemide pass, by the present process, into bases, i.e. a chemically pure crystal modification III of torasemide is obtained.

Moreover, it has been found that the new crystal modification III of torasemide is stable under normal storage conditions as well as at being subjected to increased humidity, which means that it is neither transformed into the unstable modification II of torasemide nor into the stable modification I of torasemide.

The new crystal modification III of torasemide has a characteristic X-ray powder pattern obtained by X-ray diffraction on a powder sample of the new crystal modification III of torasemide in the instrument PHILIPS PW3710 under Cu X-rays [-  $\lambda$  (CuK $\alpha_1$ ) = 1.54046 Å and  $\lambda$ (CuK $\alpha_2$ ) = 1.54439 Å]. Thus obtained characteristic spacings between lattice planes designated by »d« and expressed in Angström units and their corresponding characteristic relative intensities designated by »I/I<sub>0</sub>« and expressed in % are represented in Table 1.

Table 1

Modification III	
d(Å)	I/I <sub>0</sub> (%)
15.3898	2.8
12.5973	5.4
11.4565	5.8

WO 00/20395

PCT/HR99/00023

6

9.7973	69.8
9.5493	76.6
8.6802	28.5
8.2371	100.0
7.6351	10.2
7.3356	13.0
6.9759	1.2
6.5351	10.0
6.3240	7.9
6.1985	4.5
5.9521	0.6
5.6237	24.4
5.5623	29.7
5.4040	19.6
5.1119	10.3
4.8738	22.7
4.7865	46.9
4.6986	45.7
4.5985	17.9
4.4602	24.7
4.3405	90.0
4.2552	20.7
4.1829	19.9
4.0768	19.9
3.9377	47.1
3.8659	29.3
3.8429	35.3
3.7801	42.8

WO 00/20395

PCT/HR99/00023

7

3.7248	11.9
3.6239	31.7
3.5556	20.5
3.4825	7.8
3.4130	8.1
3.3055	15.5
3.2298	8.2
3.1786	10.7
3.1278	5.6
3.0699	7.1
3.0078	17.5
2.9549	5.1
2.9056	4.3
2.8541	1.8
2.7686	13.9
2.6988	5.7
2.6610	6.3
2.6293	7.3
2.5549	3.7
2.5236	2.0
2.4485	5.3
2.4161	6.7
2.3671	2.0
2.3133	3.6
2.2788	7.6
2.2312	3.4
2.1852	6.2
2.1468	3.0

WO 00/20395

PCT/HR99/00023

2.0957	4.7
2.0617	4.1
2.0273	3.3
1.9896	3.1
1.9688	4.1
1.9274	2.6
1.8853	2.7
1.7931	2.1
1.7449	1.0
1.7169	1.8
1.6512	1.0
1.6122	0.8
1.5601	0.8
1.5320	0.3
1.5057	0.5
1.4521	0.3
1.3773	0.6

In addition, by recording the monocrystal of the new crystal modification III of torasemide in four circle PHILIPS PW 1100/Stoe&Cie diffractometer under Mo X-rays [ $\lambda$  (MoK $\alpha$ ) = 0.71073 Å] there were obtained the basic crystallographic data for a single cell, which show in comparison with the literature data for crystal modifications I and II of torasemide [*Acta Cryst.* B34 (1978), 2659-2662 and *Acta Cryst.* B34 (1978), 1304-1310] that this is an absolutely new crystal modification III of torasemide.

The basic crystallographic data (diffraction on monocrystal) for modifications I, II and the new crystal modification III of torasemide are represented in Table 2.

WO 00/20395

PCT/HR99/00023

Table 2

Parameter	Crystal modification of torasemide		
	I	II	III
crystal composition	monoclinic	monoclinic	monoclinic
space group	P 2 <sub>1</sub> /c	P 2/n	P 2 <sub>1</sub> /c
a (Å)	13.308	20.446	11.430
b (Å)	8.223	11.615	19.090
c (Å)	31.970	16.877	16.695
β (°)	107.01	108.90	93.903
V (Å <sup>3</sup> )	3345.5	3791.9	3634.7
Z	4x2	4x2	4x2

The new crystal modification III of torasemide prepared according to the process of the present invention can be transformed by the use of common processes to the crystal modification I of torasemide, i.e. it can be used as a starting material for the preparation of known crystal modification I of torasemide.

The new crystal modification III of torasemide prepared according to the invention can be transformed to pharmaceutically acceptable salts of torasemide by the use of common processes.

The dissolution profile (USP 23) of the new crystal modification III of toresamide in water and in artificial intestinal juice in comparison to dissolution profiles of known crystal modifications I and II of toresamide, in the same fluids, shows a significant difference.

IDR ( Intrinsic Dissolution Rate) of the new crystal modification III of torasemide in a model of artifical gastric juice exceeds 1 mg cm<sup>-2</sup>min<sup>-1</sup>, which indicates a potential good bioavailability.

WO 00/20395

PCT/HR99/00023

10

The new crystal modification III of torasemide is prepared according to the process of the present invention in the form of a flowable crystal powder of a prismatic habitus, which exhibits flowability, i.e. it comes in a "free flow" form, wherein no static charge accumulation occurs.

The new crystal modification III of torasemide prepared according to the process of the present invention can be used as a suitable torasemide form as a diuretic as well as an agent for preventing heart or heart tissue damages caused by metabolic or ionic abnormalities associated with ischemia, in the treatment of thrombosis, angina pectoris, asthma, hypertension, nephroedema, pulmonary edema, primary and secondary aldosteronism, Bartter's syndrome, tumours, glaucoma, for decreasing intraocular pressure, acute or chronic bronchitis, in the treatment of cerebral edema caused by trauma, ischemia, concussion of the brain, metastases or epileptic attacks and in the treatment of nasal infections caused by allergens.

The present invention also relates to pharmaceutical forms such as tablets containing the new crystal modification III of torasemide as the active ingredient combined with one or more pharmaceutically acceptable additives such as sugar, starch, starch derivatives, cellulose, cellulose derivatives, mould release agents, and antiadhesive agents and possibly agents for flowability regulation. When using the new crystal modification III of torasemide for the preparation of pharmaceutical forms, also process steps taking place in water, e.g. granulation, can be used.

The starting materials for the process of the present invention i.e. the alkaline extract of the original reaction mixture for torasemide synthesis can be prepared according to DE 25 16 025, whereas the modifications I and II of torasemide can be prepared according to *Acta Cryst. B34* (1978), 1304-1310.

The present invention is illustrated but in no way limited by the following Examples.

WO 00/20395

PCT/HR99/00023

11

**Example 1**

Technically pure new crystal modification III of torasemide:

The original alkaline extract of the reaction mixture for torasemide synthesis (1000 ml) prepared according to DE 25 16 025 was acidified with 10% aqueous acetic acid solution under the addition of 1.4 g of a crystal modification III of torasemide. The suspension was stirred at room temperature for 90 minutes. The crystals were sucked off, washed with 1 litre of demineralized water and dried in a vacuum dryer at 50°C for 3 hours. There were obtained 125 g of a crystal modification III of torasemide, m.p. 162-165°C.

The X-ray powder pattern of the thus obtained sample corresponded to the new crystal modification III of torasemide. The content of torasemide according to the HPLC method was >99%.

**Example 2**

The crystal modification III of torasemide (1000 g) prepared according to the Example 1 was dissolved in a 10-fold amount of 5% aqueous potassium hydroxide solution and at the temperature of 20°C the obtained solution was acidified with 5% aqueous hydrochloric acid solution under the addition of 10 g of a crystal modification III of torasemide. The suspension was stirred at 20°C for 120 minutes. The crystals were sucked off, washed with 4 litres of demineralized water and dried in a vacuum dryer at 50°C for 3 hours. There were obtained 961 g of a modification III of torasemide, m.p. 165°C.

The X-ray powder pattern of the thus obtained sample corresponded to the crystal modification III of torasemide. The content of torasemide according to the HPLC method was >99.5%, i.e. it corresponded to chemically pure torasemide.

WO 00/20395

PCT/HR99/00023

12

**Example 3**

The crystal modification I of torasemide (1.00 g) prepared according to *Acta Cryst.* B34 (1978), 1304-1310 was dissolved in a 10-fold amount of 10% aqueous sodium carbonate solution and at the temperature of 15°C the obtained solution was acidified with 5% aqueous sulfuric acid solution under the addition of 0.10 g of the modification III of torasemide. The suspension was stirred at 15°C for 120 minutes. The crystals were sucked off, washed with 4 ml of demineralized water and dried in a vacuum dryer at 50°C for 3 hours. There were obtained 0.95 g of a crystal modification III of torasemide, m.p. 165-166°C.

The X-ray powder pattern of the thus obtained sample corresponded to the crystal modification III of torasemide. The content of torasemide according to the HPLC method was >99,5%, i.e. it corresponded to chemically pure torasemide.

**Example 4**

The crystal modification II of torasemide (1.00 g) prepared according to *Acta Cryst.* B34 (1978), 1304-1310 was dissolved in a 10-fold amount of 10% aqueous potassium carbonate solution and then at the temperature of 15°C the obtained solution was acidified with 5% aqueous nitric acid solution under the addition of 0.10 g of a modification III of torasemide. The suspension was stirred at 15°C for 120 minutes. The crystals were sucked off, washed with 4 ml of demineralized water and dried in a vacuum dryer at 50°C for 3 hours. There were obtained 0.96 g of a crystal modification III of torasemide, m.p. 164-166°C.

The X-ray powder pattern of the thus obtained sample corresponded to the crystal modification III of torasemide. The content of torasemide according to the HPLC method was >99,5%, i.e. it corresponded to chemically pure torasemide.

WO 00/20395

PCT/HR99/00023

13

**Example 5**

A mixture of crystal modifications I and II of torasemide (1.00 g) prepared according to *Acta Cryst.* B34 (1978), 1304-1310 was dissolved in a 10-fold amount of 10% aqueous lithium hydroxide solution and then at room temperature the obtained solution was acidified with 5% aqueous phosphoric acid solution under the addition of 0.10 g of a modification III of torasemide. The suspension was stirred at 15°C for 240 minutes. The crystals were sucked off, washed with 4 ml of demineralized water and dried in a vacuum dryer at 50°C for 3 hours. There were obtained 0.97 g of a crystal modification III of torasemide, m.p. 165-166°C.

The X-ray powder pattern of the thus obtained sample corresponded to the crystal modification III of torasemide. The content of torasemide according to the HPLC method was >99,5%, i.e. it corresponded to chemically pure torasemide.

**Example 6**

A mixture of crystal modifications I and III of torasemide (1.00 g) prepared according to *Acta Cryst.* B34 (1978), 1304-1310 and Example 1 was dissolved in a 10-fold amount of 5% aqueous potassium hydroxide solution and then at the temperature of 30°C the obtained solution was acidified with 10 % aqueous tartaric acid solution under the addition of 0.10 g of a modification III of torasemide. The suspension was stirred at 30°C for 180 minutes. The crystals were sucked off, washed with 4 ml of demineralized water and dried in a vacuum dryer at 50°C for 3 hours. There were obtained 0.93 g of a crystal modification III of torasemide, m.p. 164-166°C.

The X-ray powder pattern of the thus obtained sample corresponded to the crystal modification III of torasemide. The content of torasemide according to the HPLC method was >99,5%, i.e. it corresponded to chemically pure torasemide.

WO 00/20395

PCT/HR99/00023

14

**Example 7**

A mixture of crystal modifications II and III of torasemide (1.00 g) prepared according to *Acta Cryst.* B34 (1978), 1304-1310 and Example 1 was dissolved in a 10-fold amount of 5% aqueous sodium hydroxide solution and then at the temperature of 35°C the obtained solution was acidified with 5% aqueous propionic acid solution under the addition of 0.10 g of a modification III of torasemide. The suspension was stirred at 35°C for 90 minutes. The crystals were sucked off, washed with 4 ml of demineralized water and dried in a vacuum dryer at 50°C for 3 hours. There were obtained 0.87 g of a crystal modification III of torasemide, m.p. 165°C.

The X-ray powder pattern of the thus obtained sample corresponded to the crystal modification III of torasemide. The content of torasemide according to the HPLC method was >99,5%, i.e. it corresponded to chemically pure torasemide.

**Example 8**

A mixture of crystal modifications I, II and III of torasemide (1.00 g) prepared according to *Acta Cryst.* B34 (1978), 1304-1310 and Example 1 was dissolved in a 10-fold amount of 10% aqueous sodium carbonate solution and then at the temperature of 25°C the obtained solution was acidified with 5% aqueous p-toluenesulfonic acid solution under the addition of 0.10 g of a modification III of torasemide. The suspension was stirred at 25°C for 60 minutes. The crystals were sucked off, washed with 4 ml of demineralized water and dried in a vacuum dryer at 50°C for 3 hours. There were obtained 0.93 g of a crystal modification III of torasemide, m.p. 164-166°C.

The X-ray powder pattern of the thus obtained sample corresponded to the crystal modification III of torasemide. The content of torasemide according to the HPLC method was >99,5%, i.e. it corresponded to chemically pure torasemide.

WO 00/20395

PCT/HR99/00023

15

**Example 9**

A crystal modification I of torasemide (1.00 g) prepared according to *Acta Cryst.* B34 (1978), 1304-1310 was dissolved in a 10-fold amount of 10% aqueous potassium carbonate solution and then at the temperature of 15°C the obtained solution was stepwise acidified with 10% aqueous acetic acid solution under the simultaneous stepwise lowering of the temperature of the mixture to 0°C. At this temperature the suspension was stirred for 25 hours. The crystals were sucked off, washed with 4 ml of demineralized water and dried in a vacuum dryer at 50°C for 3 hours. There were obtained 0.94 g of a crystal modification III of torasemide, m.p. 164-166°C.

The X-ray powder pattern of the thus obtained sample corresponded to the crystal modification III of torasemide. The content of torasemide according to the HPLC method was >99,5%, i.e. it corresponded to chemically pure torasemide.

**Example 10****Production of 2.5 mg tablets:**

Torasemide of the crystal modification III was mixed with lactose and corn starch in a common manner, granulated with water, dried and sieved (granulate 1). Colloidal silicon dioxide and magnesium stearate were mixed, sieved and admixed into granulate 1. This mixture was then tabletized in a common manner. For the production of 100 000 tablets the following is required:

torasemide-crystal modification III	0.25 kg
lactose (Lactose Extra Fine Crystal HMS®)	6.05 kg
corn starch (Starch®)	1.60 kg
colloidal silicon dioxide (Aerosil 200®)	60.00 g

WO 00/20395

PCT/HR99/00023

16

magnesium stearate	40.00 g
redistilled water	1.20 kg

**Example 11**

Production of 100 mg tablets:

Torasemide of crystal modification III was mixed with lactose and corn starch and a part of magnesium stearate in a common manner. The mixture was compressed and sieved to obtain the desired grain size and distribution of grain size (granulate 1). Colloidal silicon dioxide and magnesium stearate were mixed, sieved and admixed into granulate 1. This mixture was then tabletized in a common manner. For the production of 100 000 tablets the following is required:

torasemide-crystal modification III	10.0 kg
lactose (Lactose Extra Fine Crystal HMS®)	2.0 kg
corn starch (Starch®)	7.7 kg
colloidal silicon dioxide (Aerosil 200®)	0.2 kg
magnesium stearate	0.1 kg

**Example 12**

The microcrystallinic modifications I, II and III of torasemide prepared according to *Acta Cryst. B34* (1978), 1304-1310 and Example 1 were subjected to dissolution testing in water and in artificial intestinal juice at 37 °C (USP 23) and the results are reported in Tables 3 and 4.

WO 00/20395

PCT/HR99/00023

17

Table 3: Dissolution test of torasemide in water (USP 23) (37 °C, 50 rpm, 1000 ml)

Minutes	% dissolved torasemide		
	Mod. I	Mod. II	Mod. III
0	0	0	0
10	6.7	15.1	15.6
20	13.0	27.8	28.1
30	18.5	39.2	37.7
40	23.5	48.8	43.6
50	28.5	56.3	48.5
60	32.8	65.1	51.1

Table 4: Dissolution test of torasemide in artificial intestinal juice (USP 23)  
(37 °C, 50 rpm, pH 7.5, 1000 ml)

Minutes	% dissolved torasemide		
	Mod. I	Mod. II	Mod. III
0	0	0	0
10	29.4	73.3	41.0
20	40.5	92.6	59.8
30	48.4	95.5	70.2
40	54.2	96.8	77.6
50	59.2	96.3	82.5
60	65.0	98.2	88.7

The results reported in Table 3 were plotted in Fig. 1. The results reported in Table 4 were plotted in Fig. 2.

WO 00/20395

PCT/HR99/00023

18

## Claims

1. New crystal modification III of torasemide, characterized in that the characteristic X-ray powder pattern of its sample is represented by the following spacings between lattice planes:

New crystal modification III of torasemide
d(Å)
15.3898
12.5973
11.4565
9.7973
9.5493
8.6802
8.2371
7.6351
7.3356
6.9759
6.5351
6.3240
6.1985
5.9521
5.6237
5.5623
5.4040
5.1119

WO 00/20395

PCT/HR99/00023

19

4.8738
4.7865
4.6986
4.5985
4.4602
4.3405
4.2552
4.1829
4.0768
3.9377
3.8659
3.8429
3.7801
3.7248
3.6239
3.5556
3.4825
3.4130
3.3055
3.2298
3.1786
3.1278
3.0699
3.0078
2.9549
2.9056
2.8541
2.7686

WO 00/20395

PCT/HR99/00023

20

2.6988
2.6610
2.6293
2.5549
2.5236
2.4485
2.4161
2.3671
2.3133
2.2788
2.2312
2.1852
2.1468
2.0957
2.0617
2.0273
1.9896
1.9688
1.9274
1.8853
1.7931
1.7449
1.7169
1.6512
1.6122
1.5601
1.5320
1.5057

WO 00/20395

PCT/HR99/00023

21

1.4521
1.3773

2. New crystal modification III of torasemide according to claim 1, characterized in that in accordance with X-ray diffraction on its sample monocrystal it is represented by the following basis crystallographic data:

Parameter	New crystal modification of torasemide
crystal composition	monoclinic
space group	P 2 <sub>1</sub> /c
a (Å)	11.430
b (Å)	19.090
c (Å)	16.695
β (°)	93.903
V (Å <sup>3</sup> )	3634.7
Z	4x2

3. New crystal modification III of torasemide according to claims 1-2, characterized in that it is chemically pure.
4. New crystal modification III of torasemide according to claims 1-3, characterized in that it does not contain water.
5. New crystal modification III of torasemide according to claims 1-4, characterized in that it does not contain a solvent.

WO 00/20395

PCT/HR99/00023

22

6. Process for the preparation of a new crystal modification III of torasemide according to claims 1-5, characterized in that an alkaline torasemide solution is subjected to controlled acidifying with inorganic or organic acids with or without addition of a seed crystal at a temperature between 0°C to 35°C within 15 minutes to 25 hours.

7. Process for the preparation of a new crystal modification III of torasemide according to claims 1-6, characterized in that as the alkaline torasemide solution an alkaline extract of the original reaction mixture for the synthesis of torasemide is used.

8. Process for the preparation of a new crystal modification III of torasemide according to claims 1-6, characterized in that as the alkaline torasemide solution an alkaline solution of any crystal modification I, II or III of torasemide or an alkaline solution of any mutual mixture of crystal modifications I, II or III of torasemide is used.

9. Process according to claims 1-8, characterized in that for the preparation of the alkaline torasemide solutions water solutions of lithium, sodium and potassium hydroxide and water solutions of sodium and potassium carbonate are used.

10. Process according to claims 1-9, characterized in that for acidifying inorganic acids such as hydrochloric, sulfuric, phosphoric or nitric acid or organic acids such as formic, acetic, propionic, oxalic, tartaric, methanesulfonic or p-toluensulfonic acid are used.

11. Process according to claims 1-10, characterized in that as the crystal seed crystal powder of one of the isocrystallinic substances is used, most preferably crystal powder of a crystal modification III of torasemide.

WO 00/20395

PCT/HR99/00023

23

12. A new crystal modification III of torasemide according to claims 1-11, characterized in that it is used as a raw material for the preparation of crystal modification I of torasemide.
13. A new crystal modification III of torasemide according to claims 1-11, characterized in that it is used as a raw material for the preparation of pharmaceutically acceptable salts of torasemide.
14. A new crystal modification III of torasemide according to claims 1-11, characterized in that it is used as a form of torasemide as a diuretic, as an agent for preventing heart or heart tissue damages caused by metabolic or ionic abnormalities associated with ischemia, in the treatment of thrombosis, angina pectoris, asthma, hypertension, nephroedema, pulmonary edema, primary and secondary aldosteronism, Bartter's syndrome, tumours, glaucoma, for decreasing intraocular pressure, acute or chronic bronchitis, in the treatment of cerebral edema caused by trauma, ischemia, concussion of the brain, metastases or epileptic attacks and in the treatment of nasal infections caused by allergens.
15. A pharmaceutical form, characterized in that it contains as the active ingredient the new crystal modification III of torasemide according to claims 1-11 combined for this purpose with pharmaceutically acceptable one or more carriers, additives or diluents.
16. A pharmaceutical form according to claim 15, characterized in that it is in tablet form.

WO 00/20395

PCT/HR99/00023

1/1

Fig. 1: Dissolution test of torasemide in water (USP 23)  
(37 °C, 50 rpm, 1000 ml)

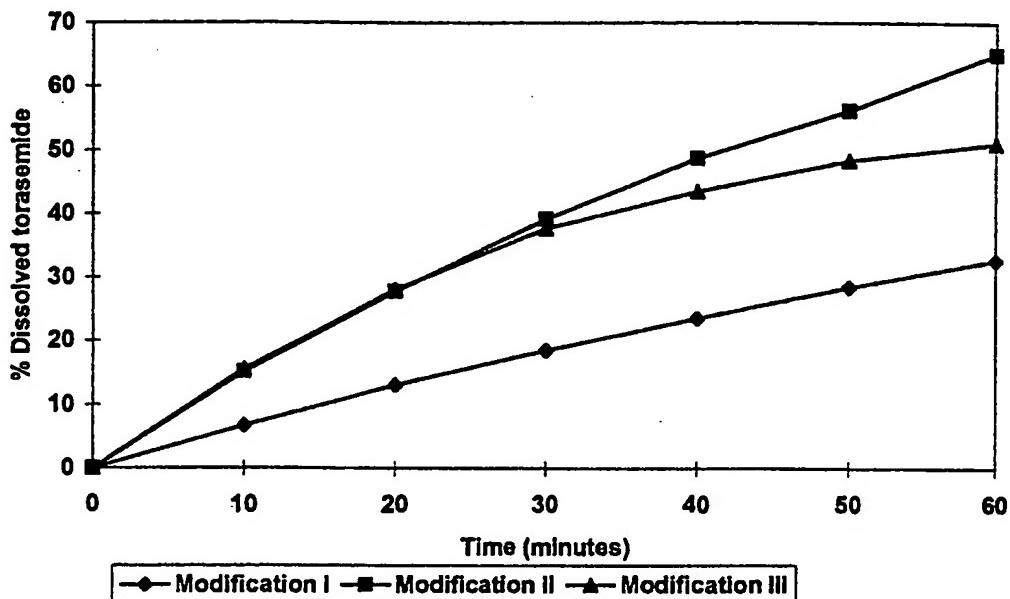
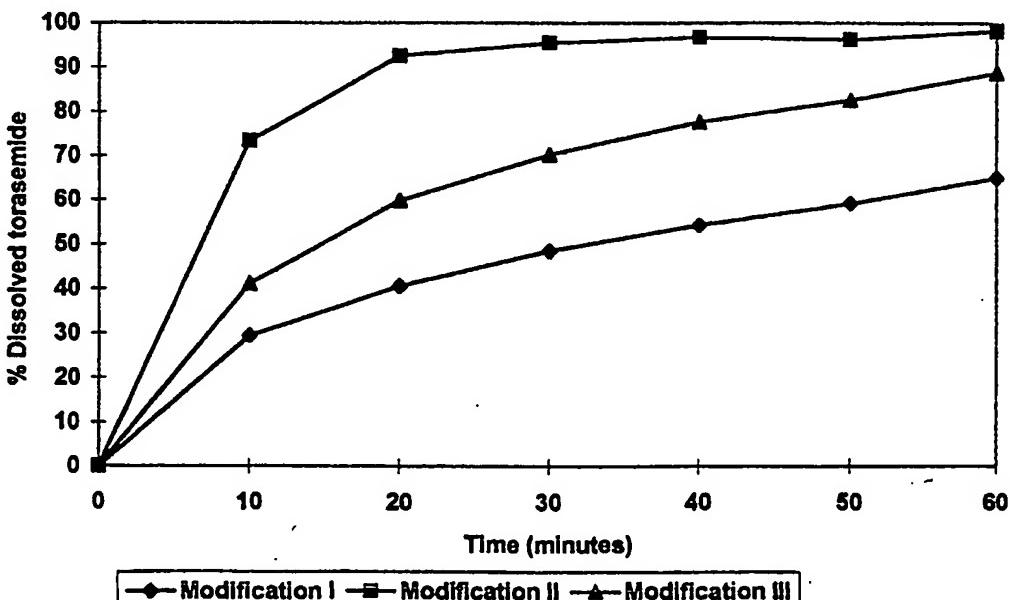


Fig. 2: Dissolution test of torasemide in artificial intestinal juice (USP 23)  
(37 °C, 50 rpm, pH 7.5, 1000 ml)



## INTERNATIONAL SEARCH REPORT

Inte	onal Application No
PCT/HR 99/00023	

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D213/74

According to International Patent Classification (IPC) or to both national classification and IPC
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B. FIELDS SEARCHED
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Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
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Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
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C. DOCUMENTS CONSIDERED TO BE RELEVANT
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Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MASEREEL B. ET AL.: "Synthesis and pharmacology of pyrid-3-ylsulfonylcyanoguanidines as diuretics" EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY. CHIMICA THERAPEUTICA, FR, EDITIONS SCIENTIFIQUE ELSEVIER, PARIS, vol. 30, no. 4, April 1995 (1995-04), pages 343-351, XP004040154 ISSN: 0223-5234 page 344, column 2 -page 345 page 350; table V ---	1-5, 12-16
P, X	US 5 914 336 A (DRECKMANN-BEHRENDT B.) 22 June 1999 (1999-06-22) column 4, line 62 -column 5, line 2 ---	1-16 -/-

<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C.
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<input checked="" type="checkbox"/> Patent family members are listed in annex.
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## \* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
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- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 January 2000	10/02/2000

Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl. Fax: (+31-70) 340-3016
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Hartrampf, G
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## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/HR 99/00023

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DUPONT L. ET AL.: "Structure cristalline et moléculaire d'un diurétique dérivé de l'alkyl-1'(phénylamo-4-pyridyl-3)sulfonyl-3 urée: la torasémide (C <sub>15</sub> H <sub>20</sub> N <sub>4</sub> S <sub>0</sub> 3)" ACTA CRYSTALLOGRAPHICA, SECTION B, vol. B34, no. 4, April 1978 (1978-04), pages 1304-1310, XP002128455 cited in the application ---	1-16
A	DUPONT L. ET AL.: "Structure d'une seconde variété de la torasémide" ACTA CRYSTALLOGRAPHICA, SECTION B, vol. B34, no. 8, August 1978 (1978-08), pages 2659-2662, XP002128456 cited in the application ---	1-16
A	EP 0 212 537 A (BOEHRINGER MANNHEIM GMBH) 4 March 1987 (1987-03-04) ---	1-16
A	KONDO N. ET AL.: "Chemical structure and physico-chemical properties of torasemide" IYAKUHIN KENKYU, vol. 25, no. 9, September 1994 (1994-09), pages 734-750, XP002128457 cited in the application -----	1-16

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No  
PCT/HR 99/00023

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
US 5914336	A	22-06-1999	NONE		
EP 0212537	A	04-03-1987	DE 3529529 A	19-02-1987	
			AT 49196 T	15-01-1990	
			AU 573454 B	09-06-1988	
			AU 6105586 A	19-02-1987	
			CA 1307277 A	08-09-1992	
			CS 9104199 A	17-06-1992	
			CS 8605945 A	15-03-1988	
			DD 259858 A	07-09-1988	
			DK 385586 A, B,	18-02-1987	
			ES 2001522 A	01-06-1988	
			FI 863305 A, B,	18-02-1987	
			GR 862139 A	30-12-1986	
			HK 59994 A	08-07-1994	
			HU 42069 A	29-06-1987	
			IE 59237 B	26-01-1994	
			IL 79672 A	18-01-1990	
			JP 1727401 C	19-01-1993	
			JP 4015205 B	17-03-1992	
			JP 62045576 A	27-02-1987	
			JP 1917095 C	23-03-1995	
			JP 2191255 A	27-07-1990	
			JP 6043400 B	08-06-1994	
			KR 9309818 B	11-10-1993	
			LT 898 A, B	27-03-1995	
			LV 5240 A	10-10-1993	
			MX 9203384 A	01-07-1992	
			NO 863305 A, B,	18-02-1987	
			NZ 217172 A	24-02-1989	
			PT 83186 A, B	01-09-1986	
			SU 1480766 A	15-05-1989	
			US RE34672 E	26-07-1994	
			US 4822807 A	18-04-1989	
			US 4743693 A	10-05-1988	
			US RE34580 E	05-04-1994	